

REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 1, 3, 5-7, 13-15, 18-21 and 24-36 will be pending in this application and presented for examination. Claims 1, 18-19, 21, 25, 27 and 30 have been amended. Claims 16 and 17 have been canceled without prejudice or disclaimer. No new matter has been entered with the foregoing amendments. Reconsideration is respectfully requested.

I. FORMALITIES

Claims 1, 21, 25, 27 and 30 have been amended to recite that the polyethylene glycol has a molecular weight of between 400-20,000. Support for the amendment is found, for example, at paragraph 81 of the published application, wherein it states:

....such as polyethylene glycol (such as Macroglol 400, Macroglol 1500, Macroglol 4000, Macroglol 6000, Macroglol 20000 (all made by Nihon Yushi))...

Applicants have included herewith the Official monographs for Macroglol 400 and Macroglol 20000 as an Exhibit. As shown therein, the average molecular weight for Macroglol 400 is about 380-420 (about 400) and for Macroglol 20000 15000-25000 (about 20000).

In view of the foregoing support, Applicants respectfully request that the amendment be entered.

In addition, claims 1, 21, 25, 27 and 30 have been amended to recite that the polyethylene oxide has a molecular weight of 2,000,000 or higher. Support for the amendment is found, for example, at paragraph 76 of the published application wherein it states:

Hydrogel-forming polymer substance used in this compression-coated solid composition means a hydrogel-forming polymer substance that causes the compression-coated tablet of the present invention to absorb the water stagnant in the upper digestive tract and thereby gel and disintegrates after a specific amount of time as it is eroded by the contractile motion of the digestive tract that accompanies digestion of food.... Consequently, a polymer substance with a higher molecular weight is preferred to form a hydrogel capable of being used with the compression-coated tablets of the

present invention. A polymer substance with a viscosity-average molecular weight of 2,000,000 or higher, further, a viscosity-average molecular weight of 4,000,000 or higher, is given as an example.

In addition, Applicants have amended claims 1, 21, 25, 27 and 30 to recite that i) the drug is metabolized by cytochrome P-450; or ii) the drug inhibits metabolism by cytochrome P-450; iii) wherein said drug is absorbed via a carrier on an epithelial cell of the small intestine. Support is found, for example, in claims 16 and 17 as filed; as well as paragraph 45 of the application as published. In view of the amendments, claims 16 and 17 have been canceled and the dependencies of claims 18 and 19 have been updated.

In view of the foregoing support, Applicants respectfully request that the amendments to the claims be entered.

II. REJECTION UNDER 35 U.S.C §112, SECOND PARAGRAPH

The Examiner rejected claims 1, 3, 5-7, 13-21, and 24-26 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Examiner alleges that there is confusion in the claims as the claims recite that there is *no* “hydrogel forming polymer” in the core, but the core recites that it contains *polyethylene glycol*. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the reaction.

In order to expedite prosecution of the present invention, Applicants have amended the claims to recite that the “polyethylene glycol” of the core has a molecular weight of between about 400-20,000. In addition, claim 1 has been further amended to recite that the term “hydrogel” forming polymer has a molecular weight of 2,000,000 or higher. The other independent claims have been updated similarly.

In view of the amendments to the claims, Applicants respectfully request that the Examiner withdraw the rejection.

In addition, the Examiner rejected claims 28 and 29 alleging that a second drug is contained within the outer layer. In response, Applicants respectfully traverse the rejection.

In the embodiments of claims 28 and 29, the second drug is *not* in the outer layer of the claimed composition. As recited in claim 28, interaction is reduced between the drug (as

recited in claim 21) and *a concomitantly used second drug*, wherein both drugs employ the same routes for drug absorption. This embodiment covers, for example, combination therapy where a second drug is being used in conjugation with the drug of claim 21. The second drug is not in the outer layer, but could be, for example, in a second formulation. In claim 29, the drug (as recited in claim 21) inhibits drug metabolism *in vivo* in humans of the second drug (as claimed in claim 28).

In view of the foregoing explanation, Applicants respectfully request that the Examiner withdraw the rejection.

III. REJECTION UNDER 35 U.S.C §102(b)

The Examiner rejected claims 1, 3, 7, 14, 15, 21, 25, 27, 30, 33, 35 and 36 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 4,925,675 ("Giannini *et al.*"). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

In order to anticipate a claim, the cited art must disclose each and every element of the claimed invention. Under MPEP § 2131:

[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

The Examiner states:

Erythromycin is mixed with a binding agent such as polyethylene glycol and *coated* to a sucrose seed creating an active core (claim 1). The active core is *coated* with a protective layer comprising a mixture of polyethylene glycol and polyethylene oxide (claims 5). The drug is present in an approximate amount of 14-40% by weight, with the polyethylene glycol in the core present in an approximate amount from 1-4% and the polyethylene glycol and oxide present in approximate amounts of 28-48% and 52-72% respectively (claims 3 and 5). [Emphasis added].

Applicants respectfully point out that the inventive tablet is completely different than the tablet architecture of Giannini *et al.* The fact that the tablets are very different is evident in Example 1, columns 10-11 of Giannini *et al.*, wherein the way and method the tablet is manufactured is described. In the method, Giannini *et al.* start with a sucrose solid core, which is then *coated* (as the Examiner has acknowledged) with successive alternating “active coating compositions” and “protective coating compositions” and finally an enteric layer. The “active coating composition” contains 3 components: i) polyethylene glycol, ii) polyethylene oxide and iii) erythromycin. The “protective coating composition” contains two components i) polyethylene glycol and ii) polyethylene oxide. Nothing about the Giannini *et al.* formulation is similar to the present invention. In Example 1 of Giannini *et al.*, there are three (3) alternating “active coating compositions,” with three (3) “protective coating compositions” coating the core. The enteric coating then encapsulates the entire tablet. The first set of alternating layers of “active coating compositions,” and “protective coating compositions” is described in lines 26-45 of column 10; the second set is described at lines 46-54 and the third set is described at line 55, bridging to column 11, lines 1-7. The enteric coat is described at 8-19 of column 11.

The core of Giannini *et al.* is solid sucrose, i.e., an *inert* sucrose seed (see, column 6, lines 14-19). There is no erythromycin or drug within the *inert* sucrose solid seed. The core of Giannini *et al.* is *coated* (as the Examiner has admitted) with an active layer containing erythromycin. The drug is not contained within the core, but the core is *coated* with erythromycin. In Giannini *et al.*, there are alternating active/protective coatings and finally an enteric coat. In operation, it would appear that after the enteric coat erodes or breaks up, the successive protective and active coats will erode, and then finally the sucrose seed would be left. As there is no erythromycin in the inert core, the core would erode without releasing erythromycin.

In contrast, the core of the present invention contains a drug and a freely erodible filler, wherein the freely erodible filler is 1 or 2 or more selected from malic acid, citric acid, tartaric acid, polyethylene glycol having a molecular weight of between 400 to 20,000, sucrose, and lactulose. The core of the inventive formulation *contains* an active agent, whereas Giannini

et al. coats the *inert* core with erythromycin. The core of the present invention is *not* inert as it contains a drug.

If the Examiner were to somehow allege that the “active coating composition” containing 3 components: i) polyethylene glycol, ii) polyethylene oxide and iii) erythromycin of Giannini *et al.* is part of the core, then the active coating composition of Giannini *et al.* also contains *polyethylene oxide*. The polyethylene oxide (if hydrogel forming) is specifically excluded from the inventive core.

As each and every element of the claim is not found in the cited art of Giannini *et al.*, Applicants respectfully request that the Examiner withdraw the rejection.

IV. REJECTION UNDER 35 U.S.C §103(a)

The Examiner rejected claims 1, 3, 5-7, 13-21 and 24-36 under 35 U.S.C. § 103(a) as allegedly being obvious over Giannini *et al.*, in view of EP 0 661 045 (“Sako *et al.*”) and EP 0 709 386 (“Taniguchi *et al.*”). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

A claim is considered obvious “if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains” (35 USC § 103(a)). The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S.Ct. 1727 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper “functional approach” to the determination of obviousness as laid down in *Graham*. The key to supporting any rejection under 35 U.S.C. § 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. § 103 should be made explicit. One of the rationales addressed by the court in *KSR* supports a finding of obviousness when the prior art reference (or combination of references) (1) teaches or suggests the claim elements; (2) provides some

suggestion or motivation to combine the references; and (3) provides a reasonable expectation of success (MPEP § 2143).

A. The cited art does not teach all the elements of the claims

The core of Giannini *et al.* is solid sucrose, i.e., an *inert* sucrose seed. There is no erythromycin or drug within the inert sucrose solid seed. The core of Giannini *et al.* is *coated* (as the Examiner has admitted) with an active layer containing erythromycin. The drug is not contained within the core, but the core is *coated* with erythromycin on its outside. In Giannini *et al.*, there are alternating active/protective coatings and finally an enteric coat. In operation, after the enteric coat erodes or breaks up, the successive protective and active coats will erode, and finally the inert sucrose seed would be left. As there is no erythromycin in the inert core, the core would erode without releasing drug.

In fact, the formulation of Giannini *et al.* actually teach away from the present invention. As taught by Giannini *et al.*, the “active coating composition” contains 3 components: i) polyethylene glycol, ii) polyethylene oxide and iii) erythromycin. That is, the coating containing the active substance *contains* polyethylene oxide. In the present invention, the active core *does not contain* polyethylene oxide. Thus, Giannini *et al.* teach that the active agent erythromycin should be formulated in the same layer as polyethylene oxide, whereas the present invention claims the active agent containing core is devoid of hydrogel forming polyethylene oxide. Thus, Giannini *et al.* teach away from the present invention.

Sako *et al.* do not supply the deficiencies of Giannini *et al.* Sako *et al.* teach a tablet that contains a *single-layer*, i.e., a homogeneous formulation which comprises a i) a drug, ii) an additive providing for the penetration of water in to the core of the preparation, and iii) a hydrogel-forming polymer. Like Giannini *et al.*, Sako *et al.* teach that the drug is in the same layer (a single layer) as polyethylene oxide. The tablet travels through the digestive system and the tablet is continuously eroded, thereby releasing the drug at every step along the way, from the upper digestive tract to the colon. The teaching of Sako *et al.* is much different than the current invention. In the embodiments of the present invention, there is an inner core and an outer layer.

Sako *et al.* do not teach or suggest an erodible core and outer layer as claimed. At least two distinct layers are present. This is in clear contrast to the disclosure of Sako *et al.*, which is a *homogenous* sustained release tablet comprising i) an active agent; ii) an additive, e.g., a hydrophilic base; and iii) a hydrogel forming polymer.

Taniguchi *et al.* teach benzazepeine compounds and pharmaceutical compositions thereof. Taniguchi *et al.* disclose a list of general pharmaceutical ingredients that can be used to formulate a tablet composition comprising the benzazepeine compounds (*see*, page 27, lines 30-37).

Giannini *et al.*, Sako *et al.*, and Taniguchi *et al.*, alone or when combined, simply do not teach or suggest the specific combination of a core comprising a drug and a freely erodible filler for the drug that is 1 or 2 or more selected from the group consisting of malic acid, citric acid and tartaric acid, polyethylene glycol, sucrose, and lactulose (without a hydrogel polymer), and the outer layer that is made from at least one type of polyethylene oxide, and polyethylene glycol. The combination of references do not teach all the features of the claims.

B. Further amendments to the claims

In order to expedite prosecution in this application, Applicants have amended the independent claims to recite that the drug is metabolized by cytochrome P-450; or the drug inhibits metabolism by cytochrome P-450; or the drug is absorbed via a carrier on an epithelial cell of the small intestine. The amendments more particularly point out and distinctly claim the subject matter by incorporating features of preferred drugs.

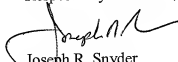
Accordingly, Applicants respectfully request that the rejection of the claims be withdrawn and for this application to be sent to issue.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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